Synthesis and immobilization of bifunctional organocatalysts, mechanistic study of organocatalytic reactions

PhD thesis

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1. Introduction

The environmentally conscious mentality, which is the endeavor to develop and apply more environmentally friendly processes, started to spread when humanity realized that the amount of waste arisen around the industrial production cannot be increased any more because it would cause serious effects. This attitude is more important in chemical industry where the resulting waste is often toxic or it can easily change environmental factors which play important roles in the physiology of living beings such as pH. In chemistry, one of the most important techniques to lower the amount of waste is using catalysis instead of equimolar reagents. It is easy to see that using less excipients will lead to producing less by-products and it can result economic benefits.

Current industrial catalytic processes mostly use transition metals, organic or inorganic derivatives of them. These methods, besides that they have the aforsaid benefits, facilitate the synthesis of chemicals which was impossible or much more complicated before. It is well known that transition metals are highly toxic and dangerous materials that is why the treatment of their waste requires special attention, especially if the product being manufactured is medicines, foods, or cosmetics, metal content has to be controlled strictly. Another problem is that these elements can be generally found in small quantities on the Earth, and also locally at low concentrations so their exploitation is costly, and involves significant destruction of nature and in the long term the sources are expected to dry up.

Due to the above-mentioned disadvantages, there is an increasing demand for the development of catalytic processes that do not contain metal. At first it seems trivial to use enzymes or their mutant variants with their high activity and selectivity, however, even the high specificity significantly reduces the range of substrates, which can be converted. With a little exaggeration a new catalyst must be produced for each reaction which, as they are macromolecules, is not easy in the design or preparative point of view. Alternatively, in the last decade a new methodology have got into the forefront of research, which essentially mimicking the functioning of the enzymes, however, using much simpler, small organic molecules as catalysts, known in the art as „organocatalysis”.

2. Aims

Bifunctional organocatalysts, previously developed in our research group, became extensively studied compounds by many research groups around the world. As a result, it was found that a very wide range of substrates, in a variety of reaction types, can be converted with high stereoselectivity with their help. Their true application-level uptake and partially the intensity of the research has been significantly inhibited by their long and small size preparation processes and by their very high commercial price. Our aim was to reduce the costs of the application of these catalysts.

First, in such a way that developing a scalable process for the preparation of catalysts common precursors epi-quinineamine and epi-quinidineamine, thereby directly reducing the cost of catalysts, and last but not least, making easier the synthesis of new catalyst candidates and finding new applications for ourselves.

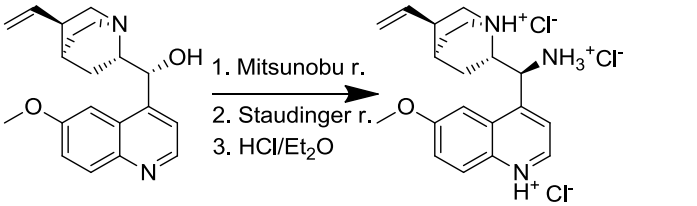
On the other hand, we decided to develop a phase nomination process for our catalysts, which makes them recyclable and it would not only reduce the cost of their application but simplify the purification of products and lower the amount of waste.

With our theoretical chemist partners, we aimed a better understanding of the functioning mechanisms of a squaramide based bifunctional organocatalyst with the combination of experimental and computational chemistry methods, primarily through the examination of the stereoselectivity determining tertiary complex. A more thorough knowing of the structure of speed-determinig transition state may help to design new molecules with higher catalytic activity.

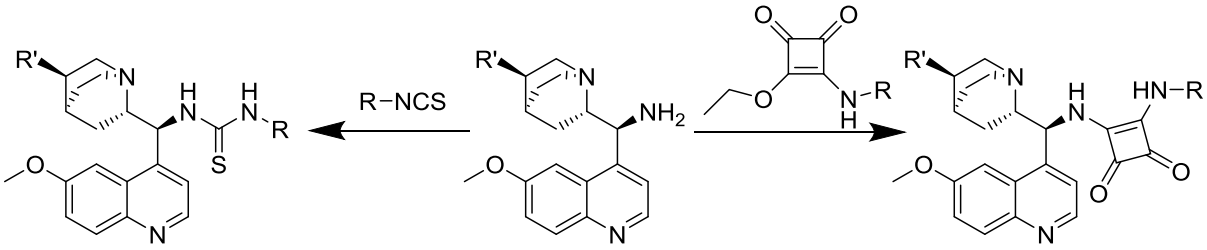
3. Results

Results of our research can be summarized in the following points.

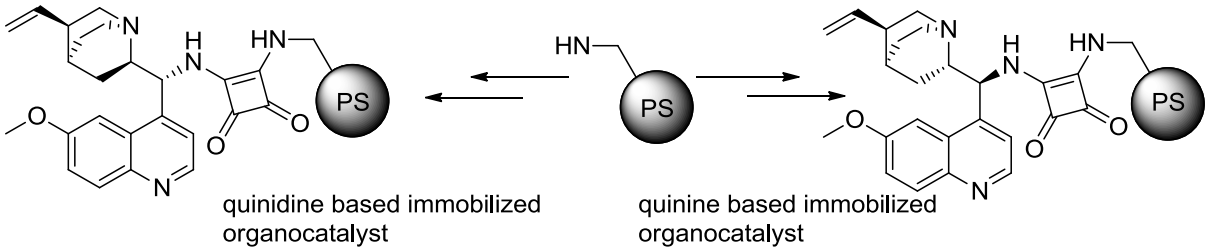
1. We have developed a scalable process for the preparation of epi-quinineamine epi-quinidineamine which are important precursors of a widely used bifunctional organocatalyst family. This method has been used in laboratory conditions with excellent reproducibility to synthetize 90 to 120 grams of high purity (> 95% HPLC) products, which can be stored for months in hydrochloride salt form without degradation.



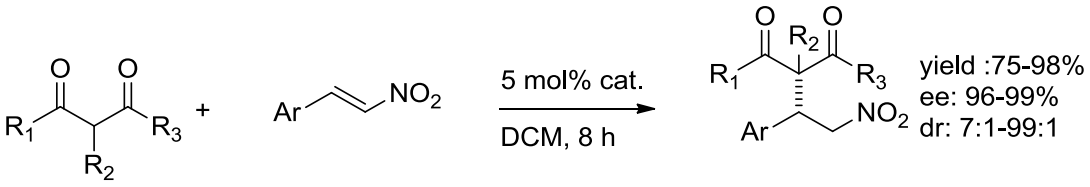
2. From the alkaloid amines, synthesized by our method, bifunctional organocatalysts were prepared. The products of the reaction did not require cleaning processes due to the quality of the corresponding starting materials.



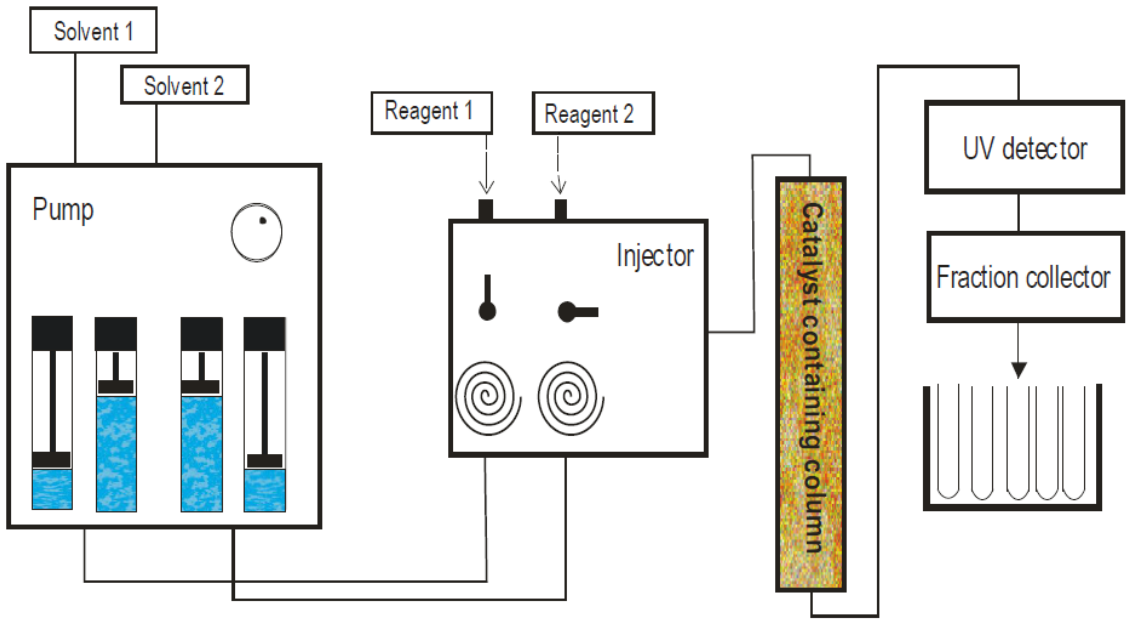
3. We have prepared immobilized organocatalysts using very simple reactions and inexpensive, commercially available polystyrene polymer resin as carrier.



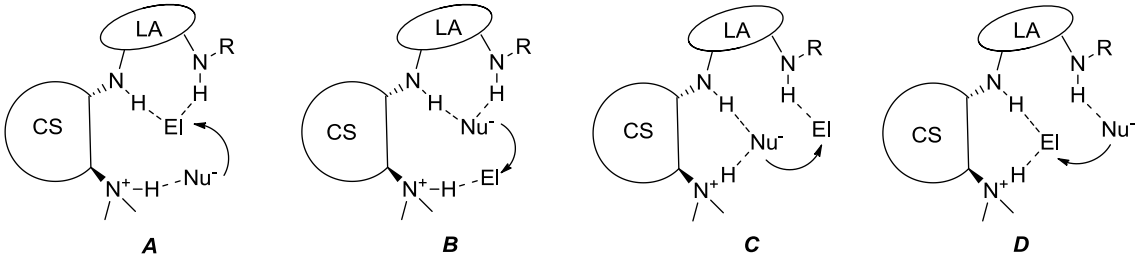
4. We have tested our solid support bound catalysts in Michael-addition reaction between nitroalkenes and 1,3-dioxo compounds. In these reactions, they have pefromed similar stereoselectivity to those soluble analogs.



5. We have prepared an organocatalyst immobilized on a macroporous polystyrene support for modeling the purpose of automation and the possibility of continuous production, and it has been tested in Michael-addition reaction in a continuous flow system. Surprisingly, we have observed increased reaction rate compared to the flask reaction without a significant change in selectivity. The catalyst has been successfully used for 16-hour continuous production and the sequential chiral synthesis of different products.

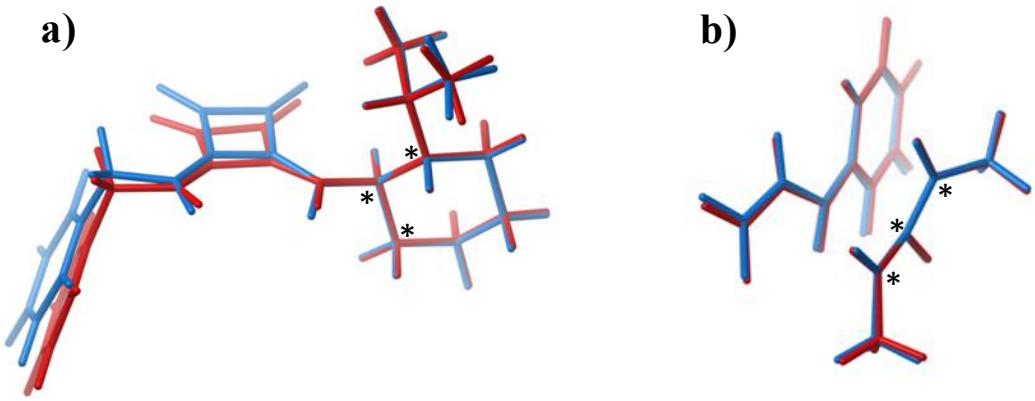


6. Possible structures of the rate determining transition state of an organocatalytic reaction has been investigated by comparing experimentally determined and theoretically calculated stereochemical parameters. We have suggested that the studied reactions prefer the route ***B*** of the possible mechanisms ***A-D***.



LA: Lewis-acidic group CS: chiral scaffold

7. The various transition states (***A*** (blue), ***B*** (red)) structures has been investigated by fragment analysis and found that both the protonated catalyst parts (a) and the anionic units leading to the product (b) show a high degree of structural invariability between different mechanism routes. This finding would significantly simplify the design of new catalysts and facilitate the calculation of the expected selectivity of a catalyst for a new reaction.



4. Publications related to the Ph.D. thesis

[1] *a)* Gy. Kardos, T. Soós, Eur. J. Org. Chem. **2013**, 4490. *b)* Synfacts, **2013**, 9, 1135.

[2] B. Kótai, Gy. Kardos, A. Hamza,V. Farkas, I. Pápai, T. Soós, Chem. Eur. J., submitted